

¹ Natural history and development of a novel composite
² endpoint in patients with alcohol-associated hepatitis:
³ Data from a prospective multicenter study

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²⁷ Abstract

²⁸ **Background & Aims:** The clinical course and outcomes of alcohol-associated hepatitis (AH)
²⁹ remain poorly understood. Major adverse liver outcomes do not capture the added risk of return
³⁰ to drinking. We examined the natural history of AH and developed a composite endpoint using
³¹ a contemporary observational cohort of AH.

³² **Approach & Results:** A cohort of 1,127 participants—712 AH patients, 256 heavy drinking
³³ controls without clinically evident liver disease, and 159 healthy controls—were prospectively
³⁴ followed for 6 months at 8 United States centers as part of the Alcoholic Hepatitis Network
³⁵ (AlcHepNet) consortium. Outcomes included mortality and a composite endpoint (AlcHep-
³⁶ Net composite index) that included death, liver transplantation, hepatic decompensation (new
³⁷ onset/worsening ascites, HE, variceal bleeding), liver-related hospital admission, MELD in-
³⁸ crease ≥ 5 , and return to drinking. Of 712 AH patients (age 45 ± 10.7 y; 59.1% male), 558
³⁹ (79.0%) had severe and 148 (21.0%) had moderate AH; 232 (32.5%) died, and 86 (12.1%)
⁴⁰ underwent liver transplantation. Mortality rates in moderate AH and severe AH were 0.7%
versus 17.2% (30 d), 3.4% versus 26.5% (90 d), and 8.8% versus 30.5% (180 d), respectively

42 (all $p < 0.001$). Composite liver/alcohol-use events were noted in 459 (64.5%) AH patients.

43 Higher MELD score, lower mean arterial pressure, and baseline leukocytosis were associated
44 with higher 90-day mortality in AH (all $p < 0.05$). College education and higher ALP were
45 associated with lower mortality. Heavy drinking controls had low mortality ($n = 3$; 1.2%).

46 **Conclusions:** This large observational study showed a high incidence of composite liver and
47 alcohol-use events within 6 months, reiterating the need for early interventions.

48 **Keywords:** alcohol-associated hepatitis; composite event; multicenter; outcomes; prospective.

49 1 INTRODUCTION

50 The prevalence, healthcare consequences, and economic impact of acute alcohol-associated hep-
51 atitis (AH) continue to increase in the United States^{1–5}. Currently, AH is the leading cause of
52 liver disease-related hospitalization and emergency room visits and accounts for nearly 20% of
53 in-hospital mortality⁵. Notably, the definition of AH used in multiple clinical studies also includes
54 patients with underlying cirrhosis^{6–9}. Recent clinical trials have reported conflicting results regard-
55 ing the impact of pharmacotherapy in severe AH^{10–13}. The Steroids Or Pentoxifylline in Alcoholic
56 Hepatitis (STOPAH) trial, conducted in Europe, reported 14%, 30%, and 57% mortality at 28 days,
57 90 days, and 1 year, respectively, in patients treated with steroids¹¹. Similarly, the Defeat Alco-
58 holic Steatohepatitis (DASH) trial conducted in the United States found mortality rates of 18%,
59 42%, and 44% at 28, 90, and 180 days, respectively, in patients with severe AH receiving corticos-
60 teroid therapy¹². In contrast, a recent trial conducted by AlcHepNet showed corticosteroid therapy
61 coupled with a stopping rule of 7-day Lille score < 0.45 ^[6] resulted in much lower mortality of
62 3%, 10%, and 19% at 30, 90, and 180 days, respectively¹³, suggesting that use of the Lille score
63 significantly lowers mortality of AH in corticosteroid-treated patients.

64 Recent epidemiological studies have reported that younger patients and those from racial and eth-
65 nic minority groups now account for an increasing proportion of AH cases^{6,14}. Sepsis and mul-
66 tiorgan failure have long been recognized as the leading causes of death in AH^{6,12,13,15}. Thus,

67 implementing hospital infection control protocols could significantly reduce the risk of adverse
68 clinical outcomes^{16,17}. The absence of placebo controls in recent clinical trials also limits our
69 understanding of the natural progression of AH. Notably, two recently completed multicenter ran-
70 domized trials in AH did not include a placebo arm^{12,13}. Observational studies generate data that
71 supplement the findings of clinical trials. The Translational Research and Evolving Alcoholic
72 Hepatitis Treatment (TREAT) study, which included 164 patients with AH and 131 concurrently
73 enrolled heavy-drinking controls without liver injury, reported a 1-year mortality of 25% in AH¹⁸.
74 However, the modest sample size limited a more comprehensive assessment of clinical outcomes in
75 AH. Composite outcomes/major adverse liver outcomes (MALOs) that include important clinical
76 events such as mortality and morbidity (decompensation, hospitalization, and return to drinking)
77 may help determine healthcare utilization and resource allocation, but have not been evaluated
78 in patients with AH. We aimed to identify critical outcomes and generate a composite outcome
79 measure highly relevant to clinical practice.

80 We present data from a prospective observational study that includes patients with both moder-
81 ate and severe AH compared to heavy drinking (HD) and healthy controls (HCs). We aimed to
82 generate a composite outcome measure that includes critical outcomes highly relevant to clinical
83 practice in patients with AH. MALOs that include liver-related deaths, liver transplant, new onset
84 development of ascites and HE, and variceal bleeding, have been suggested as relevant to clinical
85 outcomes in patients with metabolic dysfunction-associated steatotic liver disease (MASLD)¹⁹.
86 Clinically relevant events in AH also include liver-related hospital admission for worsening as-
87 cites, HE, infection, or gastrointestinal bleeding, an increase in MELD score ≥ 5 , and return to
88 drinking within 6 months, as well as MALO. Here we present a novel composite clinical endpoint
89 (AlcHepNet composite index) that offers a comprehensive, clinically relevant analysis of patients
90 with AH for use in designing future trials.

91 **2 METHODS**

92 **2.1 Study design**

93 This prospective observational study was supported by the National Institute on Alcohol Abuse
94 and Alcoholism (NIAAA) and conducted by the AlcHepNet consortium concurrently with their
95 published clinical trial^{8,13}. The study design and diagnosis criteria have been reported in previ-
96 ous publications^{8,20}. A more detailed description of the cohort is provided in the Supplemental
97 Methods and Results section (link placeholder).

98 Demographic data (age, sex, race and ethnicity, marital status, highest educational level), vital
99 signs, anthropometry, medical history, and concomitant medications; complications of portal hy-
100 pertension (ascites, jaundice, varices, HE, HCC); laboratory values with calculated Maddrey Dis-
101 criminant Function (MDF), MELD, aspartate aminotransferase to platelet ratio index (APRI), and
102 Child–Pugh (CP) scores; and HBV, HCV, or HIV status were collected. MELD scores were used
103 to classify AH severity. We defined moderate AH as MELD < 20 and severe AH as MELD ≥ 20
104 based on our prior criteria.

105 **2.2 Participants**

106 Detailed inclusion and exclusion criteria for the three groups have been reported elsewhere²⁰ and in
107 Supplemental Methods and Results (link placeholder). The study cohort included patients referred
108 from outside medical centers and were over 21 years of age. All research complied with the
109 Declarations of Helsinki and Istanbul, institutional review approvals, and written informed consent.
110 A single IRB (Western IRB–Copernicus Group, Cary, NC) approved the studies (AlcHepNet-01
111 IRB number 2018323) at all participating sites.

¹¹² **2.2.1 AH inclusion criteria**

¹¹³ Adult patients with AH defined by NIAAA consensus criteria²¹ with total bilirubin > 3 mg/dL. A
¹¹⁴ liver biopsy was done in only a small minority of patients ($n = 71$; 10%), all of whom met criteria
¹¹⁵ for definite AH. In the remaining patients ($n = 641$; 90%), the diagnosis of “Probable” AH was
¹¹⁶ based primarily on clinical criteria.

¹¹⁷ **2.2.2 AH exclusion criteria**

¹¹⁸ Etiologies of liver disease other than alcohol-associated liver disease (ALD) including hemochro-
¹¹⁹ matosis, autoimmune liver disease, Wilson disease, and viral hepatitis. The site investigator deter-
¹²⁰ mined the significance of other liver diseases. None of the patients participated in other clinical
¹²¹ trials or received off-label/experimental ALD treatments (e.g., anakinra or G-CSF). Since there
¹²² are no FDA-approved treatments for AH, corticosteroid use varied by clinical preference and was
¹²³ documented.

¹²⁴ **2.2.3 HD inclusion criteria**

¹²⁵ History of chronic heavy alcohol consumption sufficient to cause liver damage, i.e., > 40 g/d or
¹²⁶ > 280 g/wk on average for women and > 60 g/d or > 420 g/wk on average for men, but without
¹²⁷ documented liver disease.

¹²⁸ **2.2.4 HD exclusion criteria**

¹²⁹ Individuals with past evidence of ALD, defined as bilirubin > 2.0 mg/dL, AST > 1.5 × ULN,
¹³⁰ any hospital admission for liver disease, or presence of esophageal varices or ascites (at any time)
¹³¹ were excluded. AH patients were recruited in-hospital, HD patients from alcohol-rehabilitation
¹³² programs, and HC patients by advertisement.

¹³³ **2.2.5 Alcohol consumption**

¹³⁴ Timeline Follow-Back was administered systematically at baseline and each follow-up visit. The
¹³⁵ full AUDIT was administered at baseline. PEth was not collected systematically. Abstinence was
¹³⁶ defined as a binary outcome (Yes/No) based on independent assessment by the clinical team.

¹³⁷ **2.3 Outcomes**

¹³⁸ Protocol-based follow-up was for 180 days, with earlier time points to show that mortality occurred
¹³⁹ early. Early censoring markers included loss to follow-up, withdrawal, or liver transplantation
¹⁴⁰ (LT). Data were reviewed every 24 weeks to capture mortality. All-cause mortality is reported.
¹⁴¹ The **AlcHepNet composite index** comprised: (1) death (any cause up to 180 d); (2) LT (up to 180
¹⁴² d); (3) new onset of clinically detectable ascites, HE, or variceal bleeding (up to week 24 visit); (4)
¹⁴³ liver-related hospital admission (ascites, HE, infection, or GI bleeding up to 180 d); (5) increase in
¹⁴⁴ MELD ≥ 5 (to week 24); and (6) return to drinking (RTD) within 6 months.

¹⁴⁵ We also determined “recompensation” as a reduction in MELD score ≤ 5 points from enrollment
¹⁴⁶ as a surrogate improvement.

¹⁴⁷ **2.4 Statistical analysis**

¹⁴⁸ Continuous data are presented as mean \pm SD; categorical variables as percentages. Quantitative
¹⁴⁹ variables were compared using Student’s *t*-test or one-way ANOVA. Details are provided in the
¹⁵⁰ Supplemental Methods (<http://links.lww.com/HEP/K252>).

151 **3 RESULTS**

152 **3.1 Baseline characteristics of AH and HD**

153 The study cohort included 712 subjects with AH, 256 with HD, and 159 who were HC (Figure 1).
154 The demographics are shown in Table 1 and Supplemental Table S1. As expected, participants
155 with AH had significantly higher bilirubin (total and direct), serum creatinine, AST, ALT, ALP,
156 total white blood cell count (WBC), mean corpuscular volume (MCV), international normalized
157 ratio (INR), prothrombin time (PT), and lower albumin, total protein, hemoglobin, platelet count,
158 estimated glomerular filtration rate (eGFR), and mean arterial pressure (MAP) compared with
159 HD subjects (p values <0.001) (Table 1 and Supplemental Table S1). Before enrollment, 168
160 patients were started on steroids, but only 57 continued on steroids during the study (Supplemental
161 Table S2). An additional 23 patients started steroids after enrollment. Of the 80 patients who
162 received steroids during the study period, sufficient data were available to evaluate the Day 7 Lille
163 score in 69 (Supplemental Table S3). Most of our cohort had severe AH (79.0%), characterized
164 by high MELD (21.0% MELD <20 vs. 31.6% MELD 20–25, 19.4% MELD 26–30, and 28.0%
165 MELD >30), CP (10.3 ± 1.8), and MDF scores (55.1 ± 35.8) (Table 1 and Supplemental Table
166 S1 and Supplemental Figure S1). Although mean APRI scores (3.3 ± 3.4) may suggest that most
167 participants with AH had advanced fibrosis or cirrhosis (Supplemental Figure S1D), the elevated
168 value may be influenced by AST and thrombocytopenia in AH.

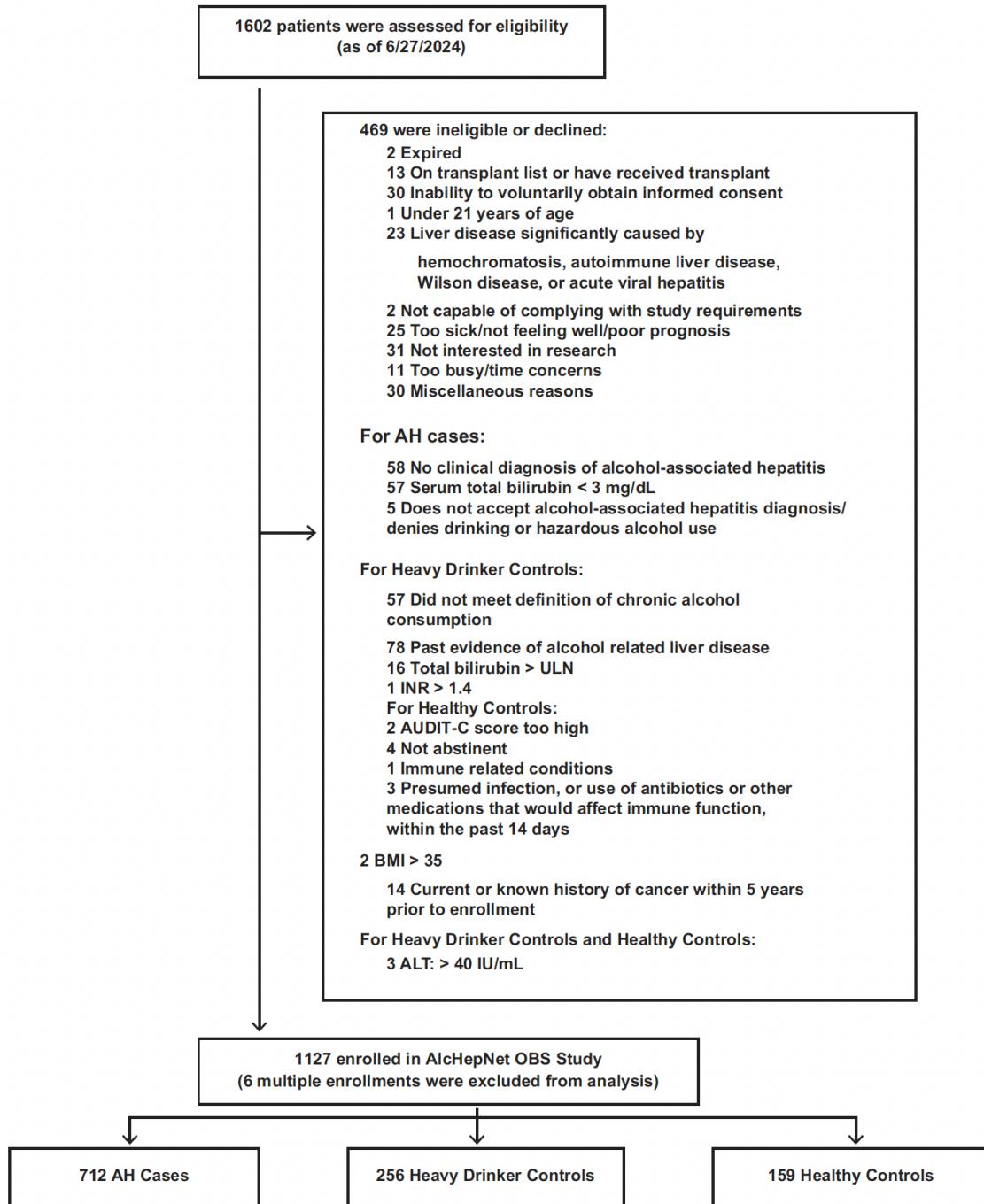


Figure 1: Participant enrollment in the AlcHepNet observational study.

Table 1: Baseline demographic and clinical characteristics of subjects

Characteristic	Subjects with AH N=712	Heavy drinkers without liver disease N=256	Healthy control N=159
Age at OBS enrollment (years)	45.0 ± 10.7	48.8 ± 13.6	36.7 ± 13.5
Sex			
Female	291 (40.9%)	109 (42.6%)	99 (62.3%)
Male	421 (59.1%)	147 (57.4%)	60 (37.7%)
Race			
Non-White	95 (13.7%)	72 (28.3%)	49 (32.7%)
White	598 (86.3%)	182 (71.7%)	101 (67.3%)
BMI (kg/m²)	29.6 ± 7.6	28.4 ± 7.5	26.4 ± 5.6
BMI (median, IQR)	28.3 (24.4, 33.4)	26.5 (23.4, 31.2)	25.3 (22.7, 29.8)
BMI category			
Normal < 25	183 (28.1%)	84 (36.4%)	68 (47.2%)
Overweight 25–30	200 (30.7%)	81 (35.1%)	44 (30.4%)
Obese ≥ 30	291 (41.3%)	66 (28.6%)	32 (22.4%)
Waist circumference (umbilicus, cm)	107.8 ± 16.7	99.0 ± 16.6	89.0 ± 15.4
Waist circumference (largest diam., cm)	109.4 ± 17.6	101.7 ± 15.9	92.1 ± 15.0
Hip circumference (cm)	105.0 ± 16.8	105.9 ± 14.7	100.3 ± 12.8
Mid-upper arm circumference (cm)	27.4 ± 5.7	30.1 ± 5.8	29.2 ± 5.0
Waist–hip ratio	1.0 ± 0.1	0.9 ± 0.1	0.9 ± 0.1

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Table 1 (continued)

Characteristic	Subjects with AH	Heavy drinkers without liver disease	Healthy control
	N=712	N=256	N=159
Education status			
No college education	272 (41.3%)	89 (35.3%)	7 (4.4%)
College education	387 (58.7%)	163 (64.7%)	151 (95.6%)
Marital status			
Not married	415 (60.1%)	173 (68.1%)	104 (65.8%)
Married	275 (39.9%)	81 (31.9%)	54 (34.2%)
Hospitalized for AH within 1 y prior to baseline visit			
No	441 (63.2%)	255 (100.0%)	157 (100.0%)
Yes	257 (36.8%)	0 (0.0%)	0 (0.0%)
Alcohol use at baseline			
No	127 (20.2%)	8 (3.2%)	81 (53.3%)
Yes	502 (79.8%)	244 (96.8%)	71 (46.7%)
Age at first drink (years)	18.7 ± 6.0	17.2 ± 7.2	18.9 ± 3.9
Total number of drinks in past 30 days	153.1 ± 197.6	238.5 ± 221.6	1.6 ± 2.5
Total number of drinking days (past 30 days)	14.9 ± 11.1	22.5 ± 9.1	1.9 ± 4.8
On steroids before or at baseline			
No	544 (76.4%)	252 (98.4%)	159 (100.0%)
Yes	168 (23.6%)	4 (1.6%)	0 (0.0%)

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Table 1 (continued)

Characteristic	Subjects with AH	Heavy drinkers without liver disease	Healthy control
	N=712	N=256	N=159
On steroids during the study			
No	632 (88.8%)	253 (98.8%)	159 (100.0%)
Yes	80 (11.2%)	3 (1.2%)	0 (0.0%)
MELD score classification			
< 20	148 (21.0%)	—	—
20–25	223 (31.3%)	—	—
26–30	137 (19.4%)	—	—
> 30	198 (28.0%)	—	—

Data are presented as mean \pm SD, median (IQR), or n (%). BMI = body mass index; MELD = Model for End-Stage Liver Disease.

¹⁶⁹ **3.2 Mortality and liver disease severity in AH**

¹⁷⁰ The median length of the follow-up was 154 days (IQR: 34.5–232.5 d). Two hundred thirty-two
¹⁷¹ (33%) of the 712 patients with AH died during follow-up. Among these, 97 (13.6%) died within 30
¹⁷² days, 153 (21.5%) died within 90 days, and 183 (25.7%) died within 180 days. The total number
¹⁷³ of deaths in participants with AH was 232, which included those who died after 180 days and
¹⁷⁴ those who died after loss to follow-up. We used Kaplan–Meier curves to depict the mortality-time
¹⁷⁵ distributions of patient groups stratified by MELD score. Mortality risk was higher with higher
¹⁷⁶ MELD scores at both 30 and 90 days (Figure 2). The unstratified overall survival and transplant-
¹⁷⁷ free survival of patients with AH at 90 days were 76.4% and 67.0%, respectively (Supplemental

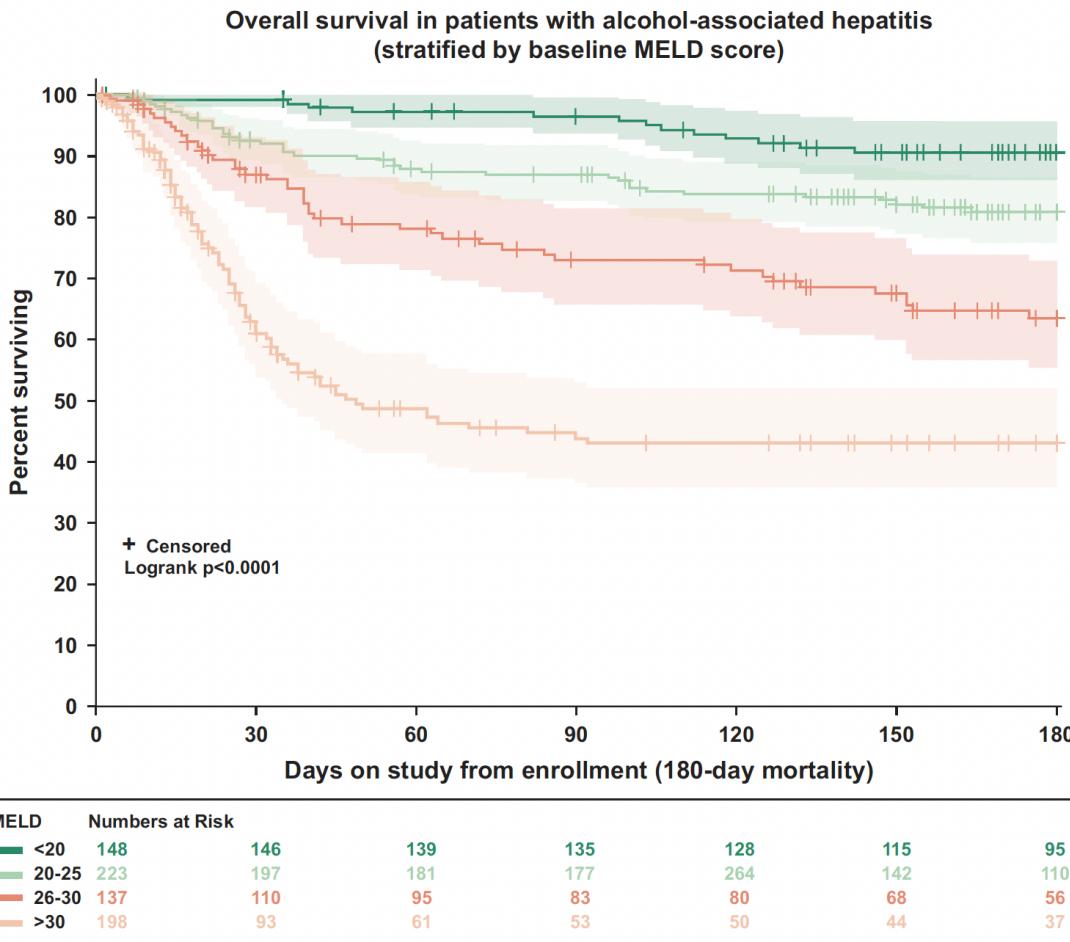


Figure 2: Kaplan–Meier curves of composite endpoints with and without return to drinking within 180 days among patients with AH.

178 Figures S2A, B).

179 We further compared the characteristics of those patients with AH who died and those who did not
 180 die within 90 days (Supplemental Table S4). Patients with AH who died were more likely to have
 181 a higher BMI (31.3 ± 7.7 vs. 29.1 ± 7.5 ; $p=0.002$), larger waist circumference (115.6 ± 20.6 cm vs.
 182 108.4 ± 16.9 cm; $p=0.012$), and elevated MELD score (32 ± 8.0 vs. 25 ± 7.8 ; $p<0.001$). They also had
 183 higher CP scores (11.0 ± 1.7 vs. 10.1 ± 1.8 ; $p<0.001$), MDF scores (76 ± 39.1 vs. 49 ± 32.5 ; $p<0.001$),
 184 total bilirubin (24.6 ± 12.1 mg/dL vs. 15.5 ± 10.9 mg/dL; $p<0.001$), serum creatinine (2.2 ± 2.1 mg/dL
 185 vs. 1.3 ± 1.5 mg/dL; $p<0.001$), total WBC count ($15.5 \pm 10.4 \times 10^9$ /L vs. $12.0 \pm 7.5 \times 10^9$ /L;
 186 $p<0.001$), INR (2.3 ± 0.7 vs. 1.9 ± 0.6 ; $p<0.001$), and PT (24.7 ± 7.7 s vs. 20.7 ± 6.1 s; $p<0.001$).
 187 Compared with the patients with AH who survived, those who died had lower eGFR (52.1 ± 32.2

¹⁸⁸ vs. 80.1 ± 39.6 ; $p < 0.001$), total protein (5.6 ± 0.9 vs. 5.9 ± 0.9 ; $p = 0.001$), hemoglobin (9.1 ± 1.9 vs. 9.4 ± 1.7 ; $p = 0.022$), platelet count ($117.1 \pm 77.8 \times 10^9 /L$ vs. $142.4 \pm 84.5 \times 10^9 /L$; $p = 0.001$), MCV (99.4 ± 8.3 vs. 101 ± 8.9 fL; $p = 0.042$), and MAP (78.4 ± 11.6 vs. 84.2 ± 11.2 mmHg; $p < 0.001$).

¹⁹¹ Among the 232 patients who died, the most frequently observed cause of death in AH was liver
¹⁹² decompensation/multiorgan failure, accounting for 47.4% of the deaths; the next most frequent
¹⁹³ specified cause of death was infection, including septic shock (7.8%), followed by renal failure
¹⁹⁴ (6.9%) (Table 2). Causes of death were unspecified in 73 of the 232 patients who died (31.5%).
¹⁹⁵ HCC was the least frequent (0.43%) cause of death in the study cohort.

Table 2: Baseline demographic and clinical characteristics of subjects (excerpt).

Characteristic	AH	HD	HC
	N=712	N=256	N=159
Age at OBS enrollment (years)	45.0 ± 10.7	48.8 ± 13.2	36.7 ± 13.5
Sex			
Female	291 (40.9%)	109 (42.6%)	99 (62.3%)
Male	421 (59.1%)	147 (57.4%)	60 (37.7%)
White, n (%)	598 (86.3%)	182 (71.7%)	101 (67.3%)
BMI (kg/m ²)	29.6 ± 7.6	28.4 ± 7.5	26.4 ± 5.6
Albumin (g/dL)	2.8 ± 0.6	4.1 ± 0.6	4.4 ± 0.4
Total bilirubin (mg/dL)	17.5 ± 11.8	0.6 ± 0.3	0.6 ± 0.4
Creatinine (mg/dL)	1.5 ± 1.7	0.9 ± 0.3	0.8 ± 0.2
AST (IU/L)	126.9 ± 73.4	35.2 ± 61.6	20.4 ± 5.8
INR	2.0 ± 0.6	1.0 ± 0.1	1.0 ± 0.1
MELD	26.5 ± 8.4	—	—

Note: Full table available in Supplemental Table S1 (link placeholder). Values are mean \pm SD or n (%).

196 The estimated effects of patient characteristics on 90-day mortality, expressed as adjusted hazard
197 ratios (aHRs) from multivariable Cox regression analysis, showed that college or higher levels of
198 education (aHR = 0.551, 95% CI: [0.352, 0.861], p= 0.0094), ALP (aHR =0.997, 95% CI:[0.994,
199 1.000]; p= 0.0328), and MAP (aHR = 0.975, 95% CI: [0.952, 0.998]; p= 0.0347) were associated
200 with reduced risk of mortality within 90 days. In contrast, higher MELD score (aHR = 1.113,
201 95% CI: [1.08, 1.15], p< 0.0001) and total WBC count (aHR =1.026, 95% CI: [1.003, 1.050];
202 p =0.0295) were associated with increased mortality risk (Table 3). Interestingly, while survival
203 was not different based on steroid use before or at enrollment, those who received steroids during
204 follow-up had significantly better survival (p < 0.0001 per log-rank test) (Supplemental Figure S3).
205 MELD scores of patients who survived improved over time across all baseline MELD strata (<20,
206 20–25, 26–30, and \geq 30), with the greatest improvement occurring between weeks 0–4 and 4–12,
207 in those with MELD scores > 30 (Supplemental Figure S4). In contrast, among those patients with
208 AH who died, MELD either remained stable or worsened in 3 of the 4 MELD strata (Supplemental
209 Figure S4). None of the HD patients developed AH or MALO at follow-up.

210 **3.3 The 3 deaths in HD patients were not due to liver-related causes**

211 Patients with AH who had decompensated liver disease (as defined in the Methods section) at
212 baseline, compared with those who had compensated liver disease at baseline, were more likely
213 to be White (87.9% vs. 81.3%, p = 0.028) and more likely to have been hospitalized due to AH
214 within 1 year before the baseline visit (39.1% vs. 29.6%). Compensated patients were more
215 likely to report alcohol use at baseline than decompensated patients (92% vs. 76%, p < 0.001)
216 (Supplemental Table S5). As expected, liver disease severity scores, as measured by MELD and
217 CP, and laboratory chemistry and hematologic values were higher in patients with decompensated
218 disease than in those with compensated disease at baseline (Supplemental Table S5).

²¹⁹ **4 DISCUSSION**

²²⁰ In this large, prospective, multicenter cohort of contemporary patients with alcohol-associated
²²¹ hepatitis (AH), short-term mortality and morbidity remained substantial. By 180 days, one in four
²²² patients had died and nearly two thirds experienced at least one event captured by the AlcHepNet
²²³ composite index, with events clustering early after enrollment. Mortality scaled with baseline
²²⁴ severity: risk was greatest among those with MELD ≥ 20 and particularly MELD > 30 , while even
²²⁵ patients with moderate AH (MELD < 20) had clinically meaningful 6-month mortality exceeding
²²⁶ 8%. These observations align with prior trials and cohorts that report high early mortality in severe
²²⁷ AH and support the prognostic value of MELD in this population^{11–13,22–24}.

²²⁸ Multivariable analyses identified higher MELD and leukocytosis as independent predictors of 90-
²²⁹ day mortality, whereas higher mean arterial pressure and college education were associated with
²³⁰ lower risk. These findings are directionally consistent with prior literature implicating organ dys-
²³¹ function, systemic inflammation, and hemodynamic instability as key drivers of early death in
²³² AH^{6,18,25–27}. The education signal may reflect social determinants of health (access, literacy, re-
²³³ sources) rather than biology; nonetheless, it highlights a targetable equity gap within AH care
²³⁴ pathways.

²³⁵ Death alone incompletely reflects disease burden and care needs in AH. The AlcHepNet com-
²³⁶ posite index integrates liver decompensation events (ascites, encephalopathy, variceal bleeding),
²³⁷ liver-related hospitalization, clinically meaningful laboratory deterioration (MELD increase ≥ 5),
²³⁸ liver transplantation (LT), and early return to drinking (RTD). Including LT recognizes that avoid-
²³⁹ ance of death may still entail substantial morbidity and resource utilization. Incorporating RTD—
²⁴⁰ though not a liver-specific event—captures a proximal behavior strongly linked to subsequent liver
²⁴¹ outcomes beyond our 180-day window²⁸. Similar composites are common in other disciplines to
²⁴² enhance power and address competing risks^{29–31}. In AH, our data show that composite events
²⁴³ accrue early (median 62 days including RTD; 92 days excluding RTD), making this endpoint both
²⁴⁴ clinically salient and trial-feasible.

245 First, the early concentration of events underscores the need for front-loaded, standardized in-
246 patient and immediate post-discharge bundles: infection prevention and early infection recogni-
247 tion^{16,17}, hemodynamic optimization, acute kidney injury avoidance, and structured transitions of
248 care. Second, systematic AUD treatment should be embedded alongside hepatology care beginning
249 at index hospitalization, given the frequency and relevance of early RTD^{14,28}. Third, risk strati-
250 fication using MELD and inflammatory markers can guide intensity and timing of interventions
251 (e.g., early specialty follow-up, closer laboratory surveillance). Although steroid exposure during
252 follow-up associated with improved survival in our cohort, this likely reflects treatment selection
253 and response (e.g., continuation after a favorable Lille score) rather than a causal effect and should
254 be interpreted cautiously in light of neutral or mixed trial findings¹¹⁻¹³.

255 LT occurred in 12% overall (11.5% by 180 days) with expected enrichment among patients with
256 higher MELD. We also observed early “recompensation,” operationalized as MELD improve-
257 ment ≤ 5 points, in roughly one third of patients. Together, these patterns suggest two diver-
258 gent short-term trajectories after presentation: rapid deterioration prompting LT versus stabi-
259 lization/improvement with supportive care. As others have noted, early LT decisions intersect
260 with disease trajectory, abstinence assessment, and inequities in access^{32,33}. Future prospec-
261 tive work should adjudicate recompensation using standardized clinical criteria (resolution of as-
262 cites/HE/bleeding) and evaluate how trajectories map to subsequent transplant candidacy and out-
263 comes^{34,35}.

264 Strengths include the large sample size, multicenter design, prospective ascertainment across both
265 moderate and severe AH, and the introduction of a pragmatic composite that captures outcomes
266 meaningful to patients and health systems. Limitations include visit-anchored follow-up that
267 precluded precise event timing; potential misclassification of causes of death; nonrandomized,
268 clinician-directed use of steroids and other therapies; binary classification of abstinence without
269 systematic biomarker confirmation (e.g., PEth); and use of MELD change as a surrogate for recom-
270 pensation. These constraints may bias effect estimates toward the null or introduce residual con-
271 founding, and they motivate the need for adjudicated endpoints and more frequent early follow-up

272 in future studies.

273 The AlcHepNet composite index provides a tractable endpoint for phase II/III AH trials powered
274 for clinically relevant morbidity, not only mortality. Next steps include (1) external validation
275 across diverse health systems; (2) sensitivity analyses weighting component severity and patient
276 relevance; (3) integration with dynamic risk models (e.g., baseline MELD, early change in biliru-
277 bin/INR/creatinine, WBC, MAP); (4) formal competing-risk and multi-state modeling to distin-
278 guish transitions (stability → decompensation → LT/death)¹⁹; and (5) incorporation of guideline-
279 concordant AUD interventions and patient-reported outcomes^{14,35}. Such designs better reflect real-
280 world goals: prevent decompensation, sustain abstinence, reduce admissions, and improve survival
281 and quality of life.

282 In a modern, U.S. multicenter cohort, AH remains characterized by high early event rates and
283 mortality tightly linked to baseline severity and systemic inflammation. A composite endpoint
284 that includes decompensation, hospitalization, MELD worsening, LT, and early RTD captures this
285 burden and is well suited for evaluating bundled hepatology–addiction care strategies. Preventing
286 early decompensation and RTD should be primary therapeutic targets in forthcoming interventional
287 studies.

288 References

- 289 1. Aslam A and Kwo PY. Epidemiology and disease burden of alcohol associated liver disease.
290 Journal of Clinical and Experimental Hepatology 2023;13:88–102.
- 291 2. Guirguis J, Chhatwal J, Dasarathy J, Rivas J, McMichael D, Nagy LE, et al. Clinical impact
292 of alcohol-related cirrhosis in the next decade: Estimates based on current epidemiological
293 trends in the United States. Alcoholism: Clinical and Experimental Research 2015;39:2085–
294 94.

- 295 3. Huang DQ, Mathurin P, Cortez-Pinto H, and Loomba R. Global epidemiology of alcohol-
296 associated cirrhosis and HCC: Trends, projections and risk factors. *Nature Reviews Gas-*
297 *troenterology & Hepatology* 2023;20:37–49.
- 298 4. Niu X, Zhu L, Xu Y, Zhang M, Hao Y, Ma L, et al. Global prevalence, incidence, and
299 outcomes of alcohol related liver diseases: A systematic review and meta-analysis. *BMC*
300 *Public Health* 2023;23:859.
- 301 5. Sengupta S, Anand A, Lopez R, Weleff J, Wang PR, Bellar A, et al. Emergency services uti-
302 lization by patients with alcohol-associated hepatitis: An analysis of national trends. *Alcohol:*
303 *Clinical and Experimental Research* 2024;48:98–109.
- 304 6. Hosseini N, Shor J, and Szabo G. Alcoholic hepatitis: A review. *Alcohol and Alcoholism*
305 2019;54:408–16.
- 306 7. Osna NA, Donohue TM, and Kharbanda KK. Alcoholic liver disease: Pathogenesis and cur-
307 rent management. *Alcohol Research* 2017;38:147–61.
- 308 8. Tu W, Gawrieh S, Dasarathy S, Mitchell MC, Simonetto DA, Patidar KR, et al. Design of a
309 multicenter randomized clinical trial for treatment of Alcohol-Associated Hepatitis. *Contem-*
310 *porary Clinical Trials Communications* 2023;32:101074.
- 311 9. Dasarathy S, Mitchell MC, Barton B, McClain CJ, Szabo G, Nagy LE, et al. Design and
312 rationale of a multicenter defeat alcoholic steatohepatitis trial (DASH): Randomized clinical
313 trial to treat alcohol-associated hepatitis. *Contemporary Clinical Trials* 2020;96:106094.
- 314 10. Forrest E, Mellor J, Stanton L, Bowers M, Ryder P, Austin A, et al. Steroids or pentoxifylline
315 for alcoholic hepatitis (STOPAH): Study protocol for a randomised controlled trial. *Trials*
316 2013;14:262.
- 317 11. Thursz MR, Richardson P, Allison M, Austin A, Bowers M, Day CP, et al. Prednisolone or
318 pentoxifylline for alcoholic hepatitis. *New England Journal of Medicine* 2015;372:1619–28.

- 319 12. Szabo G, Mitchell M, McClain CJ, Dasarathy S, Barton B, McCullough AJ, et al. IL-1 receptor antagonist plus pentoxifylline and zinc for severe alcohol-associated hepatitis. *Hepatology*
320 2022;76:1058–68.
- 322 13. Gawrieh S, Dasarathy S, Tu W, Kamath PS, Chalasani NP, McClain CJ, et al. Randomized
323 trial of anakinra plus zinc vs. prednisone for severe alcohol-associated hepatitis. *Journal of*
324 *Hepatology* 2024;80:684–93.
- 325 14. Lee BP, Witkiewitz K, Mellinger J, Anania FA, Bataller R, Cotter TG, et al. Designing clin-
326 ical trials to address alcohol use and alcohol-associated liver disease: An expert panel Con-
327 sensus Statement. *Nature Reviews Gastroenterology & Hepatology* 2024;21:626–45.
- 328 15. Liangpunsakul S. Clinical characteristics and mortality of hospitalized alcoholic hepatitis
329 patients in the United States. *Journal of Clinical Gastroenterology* 2011;45:714–9.
- 330 16. Kaur B, Rosenblatt R, and Sundaram V. Infections in alcoholic hepatitis. *Journal of Clinical*
331 *and Translational Hepatology* 2022;10:718–25.
- 332 17. Di Cola S, Gazda J, Lapenna L, Ceccarelli G, and Merli M. Infection prevention and control
333 programme and COVID-19 measures: Effects on hospital-acquired infections in patients with
334 cirrhosis. *JHEP Reports* 2023;5:100703.
- 335 18. Lourens S, Sunjaya DB, Singal A, Liangpunsakul S, Puri P, Sanyal A, et al. Acute alcoholic
336 hepatitis: Natural history and predictors of mortality using a multicenter prospective study.
337 *Mayo Clinic Proceedings: Innovations, Quality & Outcomes* 2017;1:37–48.
- 338 19. Shang Y, Akbari C, Dodd M, Zhang X, Wang T, Jemielita T, et al. Association between longi-
339 tudinal biomarkers and major adverse liver outcomes in patients with non-cirrhotic metabolic
340 dysfunction-associated steatotic liver disease. *Hepatology* 2025;81:1501–11.
- 341 20. Dasarathy S, Tu W, Bellar A, Welch N, Kettler C, Tang Q, et al. Development and evalua-
342 tion of objective trial performance metrics for multisite clinical studies: Experience from the
343 AlcHep Network. *Contemporary Clinical Trials* 2024;138:107437.

- 344 21. Crabb DW, Bataller R, Chalasani NP, Kamath PS, Lucey M, Mathurin P, et al. Standard def-
345 definitions and common data elements for clinical trials in patients with alcoholic hepatitis: Rec-
346 ommendation from the NIAAA Alcoholic Hepatitis Consortia. *Gastroenterology* 2016;150:785–
347 90.
- 348 22. Kamath PS, Wiesner RH, Malinchoc M, Kremers W, Therneau TM, Kosberg CL, et al. A
349 model to predict survival in patients with end-stage liver disease. *Hepatology* 2001;33:464–
350 70.
- 351 23. Singal AK and Kamath PS. Model for end-stage liver disease. *Journal of Clinical and Exper-
352 imental Hepatology* 2013;3:50–60.
- 353 24. Dunn W, Jamil LH, Brown LS, Wiesner RH, Kim WR, Menon KN, et al. MELD accurately
354 predicts mortality in patients with alcoholic hepatitis. *Hepatology* 2005;41:353–8.
- 355 25. Pang JX, Ross E, Borman MA, Zimmer S, Kaplan GG, Heitman SJ, et al. Risk factors
356 for mortality in patients with alcoholic hepatitis and assessment of prognostic models: A
357 population-based study. *Canadian Journal of Gastroenterology and Hepatology* 2015;29:131–
358 8.
- 359 26. Forrest E, Evans C, Stewart S, Phillips M, Oo YH, McAvoy N, et al. Analysis of factors
360 predictive of mortality in alcoholic hepatitis and derivation and validation of the Glasgow
361 alcoholic hepatitis score. *Gut* 2005;54:1174–9.
- 362 27. Kasztelan-Szczerbińska B, Słomka M, Celinski K, and Szczerbinski M. Alkaline phosphatase:
363 The next independent predictor of the poor 90-day outcome in alcoholic hepatitis. *BioMed
364 Research International* 2013;2013:614081.
- 365 28. Louvet A, Labreuche J, Artru F, Bouthors A, Rolland B, Saffers P, et al. Main drivers of
366 outcome differ between short term and long term in severe alcoholic hepatitis: A prospective
367 study. *Hepatology* 2017;66:1464–73.

- 368 29. Pitt B, Filippatos G, Agarwal R, Anker SD, Bakris GL, Rossing P, et al. Cardiovascular
369 events with finerenone in kidney disease and type 2 diabetes. *New England Journal of*
370 *Medicine* 2021;385:2252–63.
- 371 30. Bakris GL, Agarwal R, Anker SD, Pitt B, Ruilope LM, Rossing P, et al. Effect of finerenone
372 on chronic kidney disease outcomes in type 2 diabetes. *New England Journal of Medicine*
373 2020;383:2219–29.
- 374 31. SPRINT Research Group. A randomized trial of intensive versus standard blood-pressure
375 control. *New England Journal of Medicine* 2015;373:2103–16.
- 376 32. Hsu CC, Dodge JL, Weinberg E, Im G, Ko J, Davis W, et al. Multicentered study of patient
377 outcomes after declined for early liver transplantation in severe alcohol-associated hepatitis.
378 *Hepatology* 2023;77:1253–62.
- 379 33. Musto J, Stanfield D, Ley D, Lucey MR, Eickhoff J, and Rice JP. Recovery and outcomes of
380 patients denied early liver transplantation for severe alcohol-associated hepatitis. *Hepatology*
381 2022;75:104–14.
- 382 34. Hofer BS, Simbrunner B, Hartl L, Jachs M, Balcar L, Paternostro R, et al. Hepatic re-
383 compensation according to Baveno VII criteria is linked to a significant survival benefit in
384 decompensated alcohol-related cirrhosis. *Liver International* 2023;43:2220–31.
- 385 35. Jophlin LL, Singal AK, Bataller R, Wong RJ, Sauer BG, Terrault NA, et al. ACG clinical
386 guideline: Alcohol-associated liver disease. *American Journal of Gastroenterology* 2024;119:30–
387 54.